

REMARKSClaim amendments

The claims have been amended to recite a method for producing a recombinant retroviral particle which comprises a DNA sequence encoding SDI-1, a functional analogue, or a fragment thereof comprising stably transfecting a producer cell line with a retroviral vector comprising the DNA sequence and in which the producer cell line additionally harbors at least one DNA construct coding for proteins required to package the retroviral vector; a producer cell line stably transfected with the retroviral vector and DNA coding for proteins required to package the retroviral vector; capsules encapsulating the producer cell line, the capsule comprising a porous capsule wall being permeable to the retroviral particles produced by the producer cell; pharmaceutical compositions thereof; and methods of using the claimed compositions. Support for the amendments can be found, for example, in Example 4 and original Claims 1-32.

Priority documents

Applicants direct the Examiner's attention to the certified copies of PCT/EP96/04447 and DK 1157/95 being filed concurrently herewith.

Restriction Requirement

On May 3, 1999, Applicants' Attorney elected to prosecute the invention of Group I (Claims 1-4, 8-11, 13-17, 19-23, 26-28, 31 and 32) in a telephone conversation with the Examiner. Applicants affirm the election of Group 1.

Rejection of Claims 21-22 under 35 U.S.C. §101

Claims 21-23 are rejected under 35 U.S.C. §101 "because they are not limited to a new and useful process, machine, manufacture, or composition of matter" (Office Action, page 4). The Examiner further states however, that in the interest of compact prosecution, the claims have been interpreted as process claims.

Claims 21-23 have been amended to relate to a method of treating disorders or diseases responsive to the anti-proliferative activity of SDI-1, thereby obviating the rejection.

Rejection of Claims 1, 3, 4, 15, 16, 19-23, 26-28, 31 and 32 under 35 U.S.C. §112, first paragraph

Claims 1, 3, 4, 15, 16, 19-23, 26-28, 31 and 32 are rejected under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention" (Office Action, page 5).

Noting that Claims 19-23, 26-28, 31 and 32 are directed towards methods of treating cancer or restenosis using retroviruses and pharmaceutical compositions, the Examiner cites Feldman *et al.* and Crystal as showing that "the major problem of gene therapy is the inability to deliver genes and obtain effective levels of expression which is dependent on the mode of delivery and the vector" (Office Action, page 5). The Examiner further states that "it is unpredictable without specific guidance whether one will achieve expression of a gene at levels sufficient to obtain a therapeutic effect" and therefore, where there is a deficiency in the art in terms of predictability of obtaining therapeutic levels of expression, "in order to claim the benefit of therapy and to have a reasonable expectation of success in obtaining therapeutic levels of expression, the specification is required to provide embodiments or present a clear correlation between the working examples and the claimed method" (Office Action, pages 5-6). It is the Examiner's opinion that:

the specification does not provide adequate guidance correlating the results *in vitro* to results obtained *in vivo* in such a way that one of skill would have a reasonable expectation in obtaining a therapeutic level of expression of SDI-1 such that cancer or restenosis could be treated. The specification does not teach the level of SDI-1 required to obtain a therapeutic effect, the dosage, route of administration or the desired therapeutic effect such that one of skill would be able to determine how to use the retroviral vector as a pharmaceutical composition (claims 19-20). Therefore, the specification does not enable any pharmaceutical compositions, use of a retroviral vector for treatment of disease or methods of introducing retroviral particle for the purpose of therapy as claimed (Office Action, page 6).

Applicants respectfully disagree. The test of enablement is whether one of skill in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Teletronics*, 8 U.S.P.Q.2d 1217, 1233)). The court has stated that:

a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken

as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis: such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling (*In re Marzocchi & Horton* 169 U.S.P.Q. 367, 369 (CCPA 1971)).

The court further stated that:

it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *Id.* at 370.

In the specification as filed, Applicants demonstrate that a human bladder carcinoma derived cell line transfected with a gene encoding SDI-1 "showed significantly more cells in G₀/G₁ when grown in the presence of Dex after serum starvation (61%) than in the absence of SDI-1 expression (50.6%)" (specification, page 26, lines 20-22). It is reasonable to expect based on Applicants' data that producer cells stably transfected with a retroviral particle comprising a DNA sequence encoding SDI-1, retroviral particles produced by such a cell line and capsules which encapsulate such producer cell lines can be used to treat diseases or disorders responsive to the anti-proliferative activity of SDI-1. The court has clearly stated that a rigorous or an invariable exact correlation is not required (*Cross v. Iizuka* 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985)). The court has further stated that:

the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the Examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition (*In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)) (MPEP, 7th edition, 2164.02, page 2100-148).

Applicants also teach in the specification as filed that "dosage depends upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician in charge" (specification, page 19, lines 8-12). Those

of skill in the art can determine the appropriate dosage without undue experimentation.

The Examiner cites the Feldman *et al.* and Crystal references as evidence of the "unpredictability in obtaining therapeutic effects in humans using gene therapy" (Office Action, page 5). Feldman *et al.* review the "[r]esults of the principal clinical trials and new avenues for protection of restenosis" (Feldman *et al.*, page 9, column 1). Crystal discusses "examples from the available information regarding ongoing human trials" (Crystal, page 404, column 1). However, clinical data is not a requirement for patentability (*In re Brana*, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995), and neither Feldman *et al.* nor Crystal discuss the model used by Applicants to enable the claimed invention.

The Examiner has not provided evidence to show that one skilled in the art would not accept Applicants' *in vitro* data as reasonably correlating to the use of producer cells stably transfected with a retroviral particle comprising a DNA sequence encoding SDI-1, retroviral particles produced by such a cell line and capsules which encapsulate such producer cell lines to treat diseases or disorders responsive to the anti-proliferative activity of SDI-1. Applicants have provided an enabling disclosure for the full scope of the claimed invention.

The Examiner states that Claims 1, 3 and 4 "are not enabled because one of skill would not be able to determine what applicants consider to be amino acids 1-71 or 42-58 of SDI-1" (Office Action, page 6). The Examiner further states that SDI-1 is also identified as WAF1, CIP1, PIC1 or p21 and their amino acid sequences varies. The Examiner concludes that one of skill in the art would not be able to determine what applicants consider amino acids 1-71 or 42-58 of SDI-1 and furthermore, that the specification has not taught how to identify functionally useful analogues or fragments of the SDI-1 gene.

The term SDI-1 is a term of art known to those of skill in the art. Furthermore, the court has clearly indicated that the meaning of a claim is not analyzed in a vacuum, but in light of the teachings in the specification (*In re Moore and Janoski*, 169 U.S.P.Q. 236, 238 (CCPA 1971). In the specification as filed, Applicants clearly teach that the "DNA and amino acid sequence SDI-1 is described in WO-A1-95/06415" (specification, page 8, lines 20-21). Nevertheless, Claims 3 and 4 have been amended to more clearly indicate that the DNA sequence codes for particular amino acids of human SDI-1, which is clearly described in WO-A1-95 06415. Finally, those of skill in the art can identify functionally useful analogues or fragments of the SDI-1 gene, a known gene, using routine methods. As indicated by the court, a specification need not disclose,

and preferably omits, what is well known to those skilled in the art (*In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir., 1991)).

The Examiner states that Claims 15, 16 and 20 "are not enabled because the only disclosed use for such cells in the specification is for administering the cells *in vivo* for the purpose of obtaining therapeutic effects and because the administration of replication competent retroviral packaging cells would most likely result in toxic, non-therapeutic results" (Office Action, page 7).

As indicated above, based on Applicants' data in the specification as filed, it is reasonable to expect that capsules which encapsulate producer cell lines stably transfected with a retroviral particle comprising a DNA sequence encoding SDI-1 can be used to treat diseases or disorders responsive to the anti-proliferative activity of SDI-1. Furthermore, it is incumbent upon the Patent Office to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement (*Marzhoeci* at 370). The Examiner has not provided evidence to show that one skilled in the art would not accept Applicants' *in vitro* data as reasonably correlating to the use of capsules which encapsulate producer cell lines stably transfected with a retroviral particle comprising a DNA sequence encoding SDI-1 to treat diseases or disorders responsive to the anti-proliferative activity of SDI-1.

Applicants have provided an enabling disclosure for the full scope of the claimed invention.

Rejection of Claims 9-11, 21-23 and 26 under 35 U.S.C. §112, second paragraph

Claims 9-11, 21-23 and 26 are rejected under 35 U.S.C. § U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 8).

The Examiner states that Claims 9-11 "are indefinite because it is unclear whether the first 'promoter' on line 4 of claim 9 is a target cell specific regulatory promoter or if it simply promotes expression of DNA" (Office Action, page 8).

Claim 9 has been amended to indicate that the promoter is a target cell specific promoter, thus obviating the rejection.

The Examiner states that Claims 21-23 "provides for the use of a retroviral particle, but, since the claim does not set forth any steps involved in the method process, it is unclear what

method/process applicant is intended to encompass" (Office Action, page 8). The Examiner also rejects Claims 21-23 under 35 U.S.C. §101 because the claimed recitation of a use without setting forth any steps involved in the process results in an improper definition of a process.

Claims 21-23 have been amended to recite a method of treating disorders or diseases responsive to the anti-proliferative activity of SDI-1, thereby obviating both rejections.

The Examiner states that Claim 26 "is indefinite because it recites insertion of antisense, but depends from claim 17 which only recites genes encoding expressible SDI-1" (Office Action, page 8).

Claim 26 has been amended to delete the reference to antisense SDI-1 DNA and depend from Claim 13, thereby obviating the rejection.

Rejection of Claims 1-4 and 9 under 35 U.S.C. §102(b)

Claims 1-4 and 9 are rejected under 35 U.S.C. §102(b) "as being anticipated by Tsang et al. (1994, Vaccine Res., Vol. 3, pages 183-193)" (Office Action, page 9). The Examiner states that Tsang *et al.* teach retroviral vectors comprising p21 ras and mutants of p21, and "because p21 is considered to be equivalent to SDI-1", Tsang *et al.* anticipate Applicants' claimed retroviral vectors encoding SDI-1.

Tsang *et al.* demonstrate that "a T-cell specific immune response to point mutated p21 ras protein bearing a single amino acid substitution at position 12 can be elicited by in vitro stimulation with peptides reflecting the mutated portion of the transformed p21 ras protein" and that "point-mutated p21 ras peptide-specific T cells can recognize specific p21 ras mutations that can manifest CD4⁺-mediated cytotoxic responses" (Tsang *et al.*, page 190, first paragraph). The ras p21 protein is involved in signal transduction and the corresponding is a protooncogene (Tsang *et al.*, page 190, paragraphs 3 and 7). Protooncogenes participate in cell proliferation. As Tsang *et al.* notes, a single amino acid substitution "shifts the mutated ras protein to a constitutively active protein, resulting in stimulation of cell proliferation" (Tsang *et al.*, paragraph bridging pages 183-184).

In contrast, as described in the subject application, Applicants' claimed invention relates to SDI-1, a protein which inhibits cell proliferation. Clearly, the teachings of Tsang *et al.* do not anticipate Applicants' claimed invention.

Rejection of Claims 1-4 and 9 under 35 U.S.C. §102(e)

Claims 1-4 and 9 are rejected under 35 U.S.C. §102(e) "as being anticipated by Nabel *et al.* (US Patent 5,863,904, Jan 26, 1999)" (Office Action, page 9). The Examiner states that Nabel *et al.* teach adenoviral or retroviral vectors comprising p21 used to accumulate cells in G₀/G₁ and that the gene encoding p21 is considered equivalent to Applicants' claimed SDI-1 because both SDI-1 and p21 cause cells to accumulate in G₀/G₁ and the specification describes SDI-1 as p21.

Nabel *et al.* teach a method for treating cancer or restenosis comprising administering to a patient an expression vector containing the gene which encodes p21. Nabel *et al.* teach that suitable expression vectors include eukaryotic and viral vectors, including retroviral vectors (preferably with impaired ability to replicate and transform).

As amended, Applicants' claimed invention relates to a method for producing a recombinant retroviral particle, the particle comprising a DNA sequence encoding SDI-1, a functional analogue, or a fragment thereof, comprising stably transfecting a producer cell with a retroviral vector comprising the DNA sequence, the producer cell additionally harboring at least one DNA construct coding for proteins required for the retroviral vector to be packaged: a producer cell stably transfected with a retroviral vector comprising a DNA sequence encoding SDI-1, a functional analogue thereof, or a fragment thereof, said producer cell additionally harboring at least one DNA construct coding for the proteins required for said retroviral vector to be packaged: a capsule which encapsulates the producer cell, the capsule comprising a porous capsule wall being permeable to the retroviral particles produced by the producer cell: pharmaceutical compositions thereof: and methods of using the claimed compositions.

Nabel *et al.* do not teach a method for producing a recombinant retroviral particle comprising a DNA sequence encoding SDI-1, a functional analogue, or a fragment thereof, comprising stably transfecting a producer cell with a retroviral vector comprising the DNA sequence, the producer cell additionally harboring at least one DNA construct coding for proteins required for the retroviral vector to be packaged: a producer cell stably transfected with a retroviral vector comprising a DNA sequence encoding SDI-1, a functional analogue thereof, or a fragment thereof, said producer cell additionally harboring at least one DNA construct coding for the proteins required for said retroviral vector to be packaged: and a capsule encapsulating the producer cell, the capsule comprising a porous capsule wall being permeable to the retroviral particles produced by the producer cell.

Thus, Nabel *et al.* do not anticipate the subject matter of Applicants' claimed invention, particularly as amended.

Rejection of Claims 1-4, 8-11, 13-17, 19-23, 26-28, 31 and 32 under 35 U.S.C. §103(a)

Claims 1-4, 8-11, 13-17, 19-23, 26-28, 31 and 32 are rejected under 35 U.S.C. §103(a) as being unpatentable over Nabel *et al.* in view of Haertig *et al.*, Nakanishi *et al.* and Stange *et al.* (Office Action, page 10). The Examiner states that Nabel *et al.* teach adenoviral or retroviral vectors comprising p21 used to accumulate cells in G₀/G₁ and that the gene encoding p21 is considered equivalent to Applicants' claimed SDI-1 because both SDI-1 and p21 cause cells to accumulate in G₀/G₁ and the specification describes SDI-1 as p21. The Examiner further states that Nabel *et al.* teach administering the viral vectors encoding p21 to treat restenosis or breast cancer and encapsulating the viral vector in a liposome, but Nabel *et al.* do not teach using the MMTV regulatory elements. The Examiner states that Haertig *et al.* "teach the MMTV regulatory elements can be used to create a chimeric retroviral vector to obtain mammary cell-specific expression of the gene of interest" (Office Action, page 11). The Examiner states that:

[o]ne of skill in the art would have recognized the ability to improve delivery of SDI-1 by directing expression of SDI-1 to breast tissue using the MMTV regulatory elements taught by Haertig *et al.* and would have been motivated to direct expression of SDI-1 to breast cancer since both Nabel *et al.* and Haertig *et al.* are directed to vector expression in tissues of interest. As it is unclear what is considered a therapeutic effective dose or a therapeutic effect, one of ordinary skill would have had a reasonable expectation of success in merely administering a retroviral vector as claimed and obtaining some expression (Office Action, page 11).

The Examiner further states that Claims 3 and 4 are obvious in view of Nabel *et al.* because the p21 of Nabel *et al.* encodes amino acids 1-71 and 42-58 of SDI-1, and Nakanishi *et al.* teach the essential elements of SDI-1 are up to residue 71 (Claim 3) and that amino acids 49-65 can be used to make a chimeric protein (Claim 4). The Examiner states that the packaging cell lines of Claims 13 and 14 are obvious in view of Nabel *et al.* because packaging cell lines required for making retroviral vectors; the encapsulated cells of Claims 15 and 16 are obvious in view of Nabel *et al.*, Haertig *et al.* and Stange *et al.* because Stange *et al.* teach polyelectrolytes provide an improved method of delivering cells; that injecting the retroviral vector directly to the site of the tumor (Claim 31) is obvious in view of Nabel *et al.*; and that the particular variations of the vectors recited in Claim 11 are obvious variants routinely used by those of skill in the art.

As amended, Applicants claim a method for producing a recombinant retroviral particle which comprises a DNA sequence encoding SDI-1, a functional analogue, or a fragment thereof comprising stably transfecting a producer cell line with a retroviral vector comprising the DNA sequence and in which the producer cell line additionally harbors at least one DNA construct coding for proteins required to package the retroviral vector; a producer cell line stably transfected with the retroviral vector and DNA coding for proteins required to package the retroviral vector; capsules encapsulating the producer cell line, the capsule comprising a porous capsule wall being permeable to the retroviral particles produced by the producer cell; pharmaceutical compositions thereof; and methods of using the claimed compositions.

An obviousness rejection requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in applicant's disclosure." Id. The cited references, either alone or in combination, do not teach or suggest producing retroviral particles comprising a DNA sequence encoding SDI-1 or provide a reasonable expectation of doing so.

Nabel *et al.* teach a method for treating cancer or restenosis comprising administering to a patient an expression vector containing the gene which encodes p21. Nabel *et al.* teach that suitable expression vectors include eukaryotic and viral vectors, including retroviral vectors (preferably with impaired ability to replicate and transform). As discussed above, Nabel *et al.* do not teach Applicants' claimed invention, particularly as amended.

In particular, Nabel *et al.* used an adenoviral DNA vector comprising the p21 gene and the genes required for synthesis of packaging proteins and in which the E1A and E1B replicases and activators of gene expression were deleted. The deleted E1A and E1B were provided by the 293 cell line used for propagation of recombinant adenoviruses (Nabel *et al.*, column 6, lines 22-34). Generation of DNA viruses involve the packaging of the DNA with proteins provided in the vector, and release of the DNA viruses by cell lysis.

In contrast, generation of RNA viruses and retroviruses involves initially the transcription of the recombinant DNA vector into RNA. Subsequently, the RNA molecules are packaged and released by budding from the packaging cells. The protein for packaging of these viruses are provided by packaging constructs included in the packaging cell line (specification, page 10, line 24 - page 11, line 17).

During transient transfection, the vector-DNA in both DNA and RNA viruses is transient, not stably present in the packaging cell line, *i.e.*, during this period of transient transfection, the foreign vector-DNA is degraded by DNAases included in the packaging cell line and the vector-DNA is not transmitted to daughter cells during division of the packaging cells. With DNA virus-derived vectors, the packaging cells are lysed upon release of the DNA viruses. However, with RNA virus-derived vectors, the transfected vector-DNA is integrated into the packaging cell genome resulting in stably transfected producer cells, since it is also a common characteristic of retroviruses to integrate into the genome of cells. As a result, during cell division daughter cells of the parental packaging cells are provided with the recombinant vector-DNA. In this case, daughter cells also become packaging cells for their recombinant DNA, resulting in a stable population of RNA-virus producing cells. With RNA viruses, the genome-integrated recombinant DNA must at first be transcribed into RNA. The transcribed recombinant retroviral RNA is not only simply packaged into proteins but also serves as a template for further translation, *i.e.*, the retroviral RNA is recognized by the translation machinery of the packaging cell as mRNA. When including an SDI-1 gene into a retroviral vector, the SDI-1 gene is transcribed and translated into protein. However, SDI-1 is known to inhibit cell proliferation and DNA synthesis, and thus, prevent cell division. Accordingly, a person of skill in the art would not expect to get a stable population of retrovirus producing cells by stable integration of a recombinant retroviral vector comprising the SDI-1 gene. Rather, a person of skill in the art would expect that after integration of the retroviral vector into the genome of the packaging cell, division of the cell would be inhibited by virtue of the expressed SDI-1 protein, and thus, stable daughter cells which produce RNA-virus would not be generated. However, Applicants have shown that stable populations of recombinant retroviral particle producing cells stably transfected with a retroviral vector comprising SDI-1 are generated.

The remaining references do not provide what is lacking in the Nabel *et al.* reference. Haertig *et al.* "show that MMTV expression is regulated by cell density in GR mouse mammary cells but not in NIH 3T3 mouse fibroblasts"...and that this "effect is mediated by binding sites in the HRE for the transcription factors OTF1 and CTF/NFI" (Haertig *et al.*, page 814, column 1). Haertig *et al.* further teach that "[a]lthough these transcription factors are present in nuclear extracts of both GR and NIH 3T3 cells, in the NIH 3T3 cells, the cell density-regulated expression of MMTV is repressed" due to a factor in the NIH 3T3 cells which represses the cell density effect (Haertig *et al.*, page 814, column 1).

Nakanishi *et al.* performed studies "to identify the active inhibitory region(s)" of the DNA synthesis inhibitory gene p21^{Sdi1} (Nakanishi *et al.*, page 555, column 2). The results of Nakanishi *et al.* "implicate amino acids 42-71 as important for growth inhibition and suggest that the minimum amino acid sequence required for DNA synthesis inhibition spans amino acids 22-71, whereas amino acids 49-71 are involved in actual binding to Cdk2 and inhibition of kinase activity" (Nakanishi *et al.*, page 555, column 2).

Stange *et al.* describe "[t]he encapsulation of hepatocytes in polyelectrolyte complex capsules formed by sodium cellulose sulfate and PDMDAAC" which "represents a new cultivation technique" (Stange *et al.*, page 349).

Clearly, the cited art does not teach or even suggest a method for producing a recombinant retroviral particle which comprises a DNA sequence encoding SDI-1, a functional analogue, or a fragment thereof comprising stably transfecting a producer cell line with a retroviral vector comprising the DNA sequence and in which the producer cell line additionally harbors at least one DNA construct coding for proteins required to package the retroviral vector: a producer cell line stably transfected with the retroviral vector and DNA coding for proteins required to package the retroviral vector and/or uses of the claimed producer cell line. Rather, as indicated above, the art teaches away from Applicants' claimed methods and compositions.

The teachings of the cited art do not render obvious the subject matter of Applicant's claimed invention.

Rejection of Claims 1-4, 8-11 and 13-17 under 35 U.S.C. §103(a)

Claims 1-4, 8-11 and 13-17 are rejected under 35 U.S.C. §103(a) as being unpatentable over Miller *et al.* or Price *et al.* in view of Noda *et al.*, Haertig *et al.*, Nakanishi *et al.* and Stange *et al.* (Office Action, page 12). The Examiner states that Miller *et al.* teach a retrovirus encoding β -gal with a 5' LTR and a human packaging cell line harboring the retrovirus and Price *et al.* teach the BAG retrovirus for marking cells for detection. The Examiner notes, however, that Miller *et al.* and/or Price *et al.* do not teach a retroviral vector encoding SDI-1 or an MMTV regulatory element. The Examiner cites Noda *et al.* as teaching plasmids encoding SDI-1 in which expression caused the senescent phenotype and Nakanishi *et al.* as teaching that the essential elements of SDI-1 are up to residue 71 and that amino acids 49-65 can be used to make a chimeric protein. The Examiner cites Haertig *et al.* as teaching that the MMTV regulatory

elements can be used to create a chimeric retroviral vector to obtain mammary cell-specific expression of the gene of interest. The Examiner states that:

it would have been obvious to combine the retroviral vector of Miller *et al.* or Price *et al.* with the SDI-1 gene of Noda *et al.* and the MMTV regulatory elements of Haertig *et al.* to obtain mammary cell tissue-specific expression of SDI-1. One of skill would have recognized the ability to direct expression of SDI-1 to breast cell lines using the MMTV regulatory elements taught by Haertig *et al.* and would have been motivated to direct expression of SDI-1 to breast tissue cell lines to study breast cancer (Office Action, page 8).

The Examiner further states that the packaging cell lines of Claims 13 and 14 are obvious in view of Nabel *et al.* because packaging cell lines required for making retroviral vectors; the encapsulated cells of Claims 15 and 16 are obvious in view of Stange *et al.* because Stange *et al.* teach polyelectrolytes provide an improved method of delivering cells; and that the particular variations of the vectors recited in Claim 11 are obvious variants routinely used by those of skill in the art.

Applicants' claimed invention as amended has been discussed above. The cited references, either alone or in combination, do not teach or suggest producing retroviral particles comprising a DNA sequence encoding SDI-1 or provide a reasonable expectation of doing so.

Miller *et al.* "describe a set of murine retrovirus-based vectors that include unique cloning sites for insertion of cDNAs such that the cDNA can be driven by either the long terminal repeat, the immediate early promoter of human cytomegalovirus, or the simian virus 40 early promoter" (Miller *et al.*, page 980, abstract).

Price *et al.* "constructed a vector containing the bacterial β -gal gene, and . . . show that this vector is capable of infection and expression of β -gal and resistance to G418 in a variety of neural cell types" (Price *et al.*, page 158, column 2).

Noda *et al.* "cloned three inhibitors of DNA synthesis from senescent cells using a functional assay" (Noda *et al.*, page 97, column 2). The remaining references (Haertig *et al.*, Nakanishi *et al.* and Stange *et al.*) have been discussed above.

Clearly, the cited art does not teach or even suggest a method for producing a recombinant retroviral particle which comprises a DNA sequence encoding SDI-1, a functional analogue, or a fragment thereof comprising stably transfecting a producer cell line with a retroviral vector comprising the DNA sequence and in which the producer cell line additionally harbors at least one DNA construct coding for proteins required to package the retroviral vector; a producer cell line stably transfected with the retroviral vector and DNA coding for proteins

required to package the retroviral vector and/or uses of the claimed producer cell line. Rather, as indicated above, the art teaches away from Applicants' claimed methods and compositions.

The teachings of the cited art do not render obvious the subject matter of Applicant's claimed invention.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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